REMARKS

Claims 113 to 127, 129 to 135 and 142 to 149 are pending in this application. Claims 113, 116, 118, 120, 124, 127, 130, 133, 142, 143, 148 and 149 have been amended. Claims 117, 122, 123, 128, 129, 132 and 140 have been canceled. The amendments to the claims are discussed below.

No new matter is added by any of the foregoing amendments to the claims.

Applicants have amended the specification on page 25, lines 20 to 29, to correct a typographical error in the journal number from 250 to 260 in the citation to Low et al., J. Mol. Biol., 260, 359-368 (1996). No new matter has been added by this amendment to the specification.

Applicants acknowledge the Examiner's withdrawal of the previous rejections of claim 144 under 35 U.S.C. § 112, second paragraph, claims 113 to 123 under 35 U.S.C. § 112, first paragraph, and of claims 113 to 116 and 122 to 123 under 35 U.S.C. § 102(b).

Applicants have also noted the Examiner's conclusion that claims 145 to 149 appear to be free of the prior art, but are objected for being dependent from a rejected independent claim.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claim 144 has been rejected for lack of enablement. The Examiner states that is unclear whether a cell line which produces an antibody having the exact chemical identity of 5/44 can be reproducibly isolated without undue experimentation and suggests that a suitable deposit for patent purposes be made. As the Examiner has noted elsewhere in the Office Action, the level of skill in the art is high and applicants submit that it would not require undue experimentation for one of ordinary skill in the art to make the 5/44 antibody. Although applicants believe that there is adequate written description to support claim 144, in the interest of expediting prosecution, applicants have canceled this claim thereby rendering this rejection moot. Applicants reserve the right to pursue this canceled claim in a continuation application(s).

Claims 113 to 116 and 122 to 123 have been rejected for lack of enablement. The Examiner states that the specification does not reasonably provide enablement for a method of treating a subject with any and/or all cancers including, but not limited to, sarcoma or carcinomas comprising administering a therapeutically effective dose of a monomeric cytotoxic drug derivative/anti-CD22 antibody conjugate. The Examiner does state, however, that the specification is enabling for a method of treating a subject with a B-cell malignancy such as leukemia or lymphoma comprising administering a therapeutically effective dose of a monomeric cytotoxic drug derivative/anti-CD22 antibody conjugate. Although applicants believe that there is adequate written description to support claims directed to methods of treating a subject with any and/or all cancers including, but not limited to, sarcoma or carcinomas comprising administering a therapeutically effective dose of a monomeric cytotoxic drug derivative/anti-CD22 antibody conjugate, applicants have, in the interest of expediting prosecution, amended claim 113 to claim a method of treating a B-cell malignancy (claims 114 to 116 are dependent on claim 113) and have canceled claims 122 to 123. Applicants submit that claims 113 to 116 are enabled and respectfully request the Examiner to reconsider and withdraw the rejection of claims 113 to 116 and 122 to 123 under 35 U.S.C. § 112, first paragraph.

By reason of the foregoing, applicants respectfully request the Examiner to reconsider and withdraw the rejections of claims 113 to 116, 122 to 123 and 144 under 35 U.S.C. § 112, first paragraph.

Rejections Under 35 U.S.C. §102(b)

A. First Rejection Under 35 U.S.C. §102(b)

The Examiner has maintained his rejection of claim 113 under 35 U.S.C. §102(b) as being anticipated by Ghetie et al. (Blood 1992; 80:2315-2320), as evidenced by Newton et al. (Blood 2001; 97: 528-535). Specifically, the Examiner states that Ghetie et al. teach a method of treating a lymphoma, comprising administering a therapeutically effective amount of a cytotoxic drug/carrier conjugate referred to as RFB4-dgA, where deglycosylated ricin A chain is the cytotoxic drug and the carrier is an antibody directed against the CD22 antigen. The Examiner further states that Ghetie et al. teach a method of treating disseminated Daudi lymphoma by administering a therapeutically effective amount of the RFB4-dgA conjugate with

an anti-CD19 antibody. The Examiner cites Newton et al. to show that Daudi lymphoma is a B cell malignancy.

Claim 113 as amended is directed to a method of treatment of a subject with a B-cell malignancy comprising administering to the subject a therapeutically effective dose of a composition comprising a monomeric cytotoxic drug derivative/anti-CD22 antibody conjugate with a reduced low conjugated fraction below 10 percent. Ghetie et al. does not teach a method of treating a subject with a B-cell malignancy that comprises administering to the subject a therapeutically effective dose of a composition comprising a monomeric cytotoxic drug derivative/anti-CD22 antibody conjugate with a reduced low conjugated fraction below 10 percent. There is no teaching in Ghetie et al. that the cytotoxicic drug/carrier conjugate has a low conjugated fraction below 10 percent. The composition used in the claimed methods with its reduced low conjugated fraction below ten percent has a different physical characteristic that is not described in Gehtie et al. nor is it inherent from Gehtie et al.'s teachings. Applicants submit that Ghetie et al. does not teach every element of the claimed invention in claim 113.

By reason of the foregoing, applicants respectfully request the Examiner to reconsider and withdraw the rejection of claim 113 as anticipated under 35 U.S.C. §102(b).

B. Second Rejection Under 35 U.S.C. §102(b)

The Examiner has maintained his rejection of claims 113 to 121 under 35 U.S.C. §102(b) as being anticipated by Uhr et al. (U.S. Patent No. 5,686,072). Specifically, the Examiner states that Uhr et al. teach a method of treating a B cell malignancy, including leukemia and Non-Hodgkin's lymphoma, comprising administering to a patient a therapeutically effective amount of an anti-CD19 antibody and anti-CD22 immunotoxin. The Examiner further states that patients include humans and the combination can be administered intravenously.

Uhr et al. defines an immunotoxin as a conjugate comprising an antibody directed against a specific cell surface molecule that has been coupled to one or more toxin molecules (see, col. 4, lines 40-42). In regard to the toxin components of the immunotoxin, Uhr et al. states that included in the term "toxin" are the commonly designated toxins such as poisonous lectins, ricin, abrin, modeccin, botulina and diphtheria toxins, as well as other toxic agents such as radio-isotopes, cytotoxic and carcinostatic drugs and combinations of the various toxins that

could also be coupled to one antibody molecule (see, col. 4, line 67 - col. 5, line 6). Preferred toxin components for use in Uhr et al. are the A chain portions of the above toxins, with ricin A chain being particularly preferred, and deglycosylated ricin A chain being even more particularly preferred (see, col. 5, lines 7-10).

Claims 113 to 121 are directed to a method of treatment of a subject comprising administering to the subject a therapeutically effective dose of a composition comprising a monomeric cytotoxic drug derivative/anti-CD22 antibody conjugate with a reduced low conjugated fraction below 10 percent. Claims 114 to 121 depend from claim 113. There is no teaching in Uhr et al. that the cytotoxicic drug/carrier conjugate has a low conjugated fraction below 10 percent. The composition used in the claimed methods with its reduced low conjugated fraction below ten percent has a different physical characteristic that is not described in Uhr et al. nor is it inherent from Uhr et al.'s teachings. Applicants submit that Uhr et al. does not teach every element of the claimed inventions in claims 113 to 121.

By reason of the foregoing, applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 113 to 121 as anticipated under 35 U.S.C. §102(b).

C. Third Rejection Under 35 US.C. §102(b)

The Examiner has maintained his rejection of claims 113 to 121 under 35 U.S.C. §102(b) as being anticipated by Goldenberg (U.S. Patent No. 6,183,744).

The Examiner states that Goldenberg teaches a method of treating a B cell malignancy in a patient comprising a therapeutically effective amount of an anti-CD22 antibody immunoconjugate, wherein the immunoconjugate is a conjugate of an antibody component with a therapeutic agent, citing column 4, lines 25-26 and column 11, lines 5-8. The Examiner states next that Goldenberg teaches that anti-CD22 antibody immunoconjugates can be used to treat both indolent and aggressive forms of Non-Hodgkin's lymphoma (col. 11, lines 11-14), and that the immunoconjugates are useful for the treatment of chronic lymphatic leukemias and acute lymphatic leukemias (col. 11, lines 8-11). The Examiner further states that regarding the therapeutic agent of the immunoconjugate, Goldenberg teaches that useful therapeutic agents for the preparation of the immunoconjugate include, but are not limited to, cancer

chemotherapeutic drugs such as nitrogen mustards, alkyl sulfonates, nitrosoureas, triazenes and folic acid analogs. No enediyne compounds, such as calicheamicin, are mentioned in Goldenberg. The Examiner also notes that Goldenberg teaches that the immunoconjugates can be administered intravenously (col. 14, lines 8-15).

Claims 113 to 121 are directed to methods of treatment of a subject comprising administering to the subject a therapeutically effective dose of a composition comprising a monomeric cytotoxic drug/carrier conjugate in which the carrier is an anti-CD22 antibody, which has a reduced low conjugated fraction below ten percent. The composition used in the claimed methods with its reduced low conjugated fraction below ten percent has a different physical characteristic that is not described in Goldenberg nor is it inherent from the teachings of Goldenberg. Goldenberg does not teach every element of the claimed methods of treatment in which therapeutically effective amounts of cytotoxic drug-anti-CD22-antibody conjugate compositions with a reduced low conjugated fraction below ten percent are administered to patients. Applicants respectfully submit that Goldenberg does not anticipate the claimed methods of treatment of claims 113 to 121.

By reason of the foregoing, applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 113 to 121 as anticipated under 35 U.S.C. §102(b).

Rejections under 35 U.S.C. §103(a)

Claims 124 to 127, 129 to 133 and 142 to 143 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Goldenberg (U.S. Patent No. 6,183,744) in view of Trail et al. (Current Opinion in Immunology 1999, 11: 584-588). Claims 134 to 135 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Goldenberg (U.S. Patent No. 6,183,744) in view of Trail et al. (Current Opinion in Immunology 1999, 11: 584-588), and in further view of Maloney et al. (Blood 1997, 90:2188-2195). As claims 129 and 132 have been canceled, the rejection is moot as to those claims.

The Examiner states that the primary reference, Goldenberg, teaches a method of treating a B cell malignancy in a patient comprising a therapeutically effective amount of an anti-CD22 antibody immunoconjugate, wherein the immunoconjugate is a conjugate of an antibody

component with a therapeutic agent, citing column 4, lines 25-26 and column 11, lines 5-8. The Examiner states next that Goldenberg teaches that anti-CD22 antibody immunoconjugates can be used to treat both indolent and aggressive forms of Non-Hodgkin's lymphoma (column 11, lines 11-14), and that the immunoconjugates are useful for the treatment of chronic lymphatic leukemias and acute lymphatic leukemias (column 11, lines 8-11). The Examiner further states that regarding the therapeutic agent of the immunoconjugate, Goldenberg teaches that useful therapeutic agents for the preparation of the immunoconjugate include, but are not limited to, cancer chemotherapeutic drugs such as nitrogen mustards, alkyl sulfonates, nitrosoureas, triazenes and folic acid analogs.

The Examiner acknowledges that Goldenberg does not explicitly teach that the therapeutic agent can be calicheamicin as in the conjugates employed in the methods of claims 124 to 127, 129 to 135 and 142 to 143. Goldenberg clearly does not teach or suggest the claimed methods of treatment in which the calicheamicin-anti-CD22-antibody conjugate compositions are administered to subjects with a B-cell malignancy. Applicants respectfully submit that Goldenberg, alone or in combination with Trail et al. or Maloney et al. discussed below, does not teach or suggest the claimed methods of treatment in which therapeutically effective amounts of calicheamicin-anti-CD22 antibody conjugate compositions are administered to subjects with a B-cell malignancy.

The Examiner states that the Trail et al. article teaches monoclonal antibody drug conjugates in the treatment of cancer. The Examiner further states that specifically, the reference teaches that members of the enediyne family of antibiotics such as calicheamicin are among the most toxic antitumor compounds described to date, but their utility as antitumor drugs has for the most part been limited by their low therapeutic index. Finally, the Examiner states that this cited reference further teaches that antibody directed delivery provides a potential means to exploit the potency of these compounds while minimizing their systemic toxicity [emphasis added]. The Examiner asserts that one of ordinary skill in the art would have a reasonable expectation of success that by administering a conjugate comprising calicheamicin and an anti-CD22 antibody to a subject with a B-cell malignancy, one would achieve an effective method of treatment. Applicants respectfully disagree.

It is not routine practice to treat a subject with a B-cell malignancy by administering a composition comprising a cytotoxic drug-antibody conjugate, including a calicheamicin-anti-CD22-antibody-conjugate, alone or with one or more cytotoxic or bioactive agents. Trail et al., cited by the Examiner, state on page 586:

> Although immunoconjugates are not currently established chemotherapeutic agents, several of them have demonstrated evidence of biologic activity in patients with advanced disease. The current objectives are aimed at improving the efficacy and therapeutic index of immunoconjugates by optimizing selectivity and potency. . . . . The calicheamicin conjugate CMA-676 [5••] has shown encouraging data in a Phase I trial of patients with refractory AML. Although immunoconjugates may be active as single agents, it is likely that their major role - especially in treatment of solid tumors - will be in combination-chemotherapy regimens or minimal-disease settings. In addition to research efforts directed at improving immunoconjugate constructs, clinical studies to define optimal therapeutic strategies are underway and will further clarify the role of immunoconjugates as anticancer agents. [emphasis added]

CMA-676 referred to in the Trail et al. paper was approved by the FDA on May 17, 2000 as the first antibody-targeted chemotherapeutic agent, and is sold under the name MYLOTARG® for treatment of patients with CD33 positive acute myeloid leukemia in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy. Yet several years later MYLOTARG® continues to be the only approved antibody-targeted chemotherapeutic agent. See, Hamann et al., Bioconjugate Chem., 2002, 13, 40-46; MYLOTARG® labeling; FDA Approval Letter, NDA 21-174, May 17, 2000 (copies attached). CMB-401, an anti-MUC1 (CT-M-01) calicheamicin conjugate discussed in Hinman et al., Cancer Res., 1993, 53, 3336-3342 (copy attached), showed only limited evidence of activity in clinical trials for ovarian cancer and lung cancer, in contrast to the demonstrated activity of MYLOTARG® in the treatment of patients with acute myeloid leukemia. See, Hamann et al., Bioconjugate Chem., 2005, 16, 354, 357 (copy attached). The activity profile of the CT-M-01 antibody calicheamicin conjugate that Hinman et al. stated in the Cancer Research

article at 3341 would need to be established, was subsequently found to be limited as described in Hamann et al., Bioconjugate Chem., 2005, 16, 354-360.

The paper authored by Hamann et al., Bioconjugate Chem., 2002, 13, 40-46 provides additional evidence that it is incorrect to assume that one of ordinary skill in the art would have a reasonable expectation of success of achieving an effective method of treatment of a subject with a B-cell malignancy by administering a conjugate comprising calicheamicin and an anti-CD22 antibody. In Hamann et al., Bioconjugate Chem., 2002, 13, 40-46, the authors discuss a comparison of two classes of calicheamicin-antibody conjugates made with an anti-CD33 antibody P67.6 and contrast them with calicheamicin conjugates made with a CTM01 antibody. The authors noted in this 2002 paper that antibody-targeted chemotherapy had been studied for many years by numerous academic and pharmaceutical groups and, in addition to having an antibody that targets a pertinent, internalizing antigen, two major criteria need to be satisfied for activity: (1) the antigen must be capable of carrying enough of the drug into the cell to deliver a toxic dose; and (2) a mechanism must be incorporated into the conjugate design to allow for drug release after internalization into the target cells. Hamann et al., Bioconjugate Chem., 2002, 13, at 44. After reviewing the experimental data reported in this paper, the authors concluded:

> The combined results for these two antibodies indicate that one optimal design of conjugate does not exist for all antibodies. Each antibody must be examined separately, and a variety of different types of conjugates must be tried in order to individually optimize a specific delivery system. The contrasting results obtained with the anti-P67.6 and anti-MUC-1 antibody conjugates probably depend more on the physiology of the target cells and the antigen that is targeted than on any specific properties of the antibodies or cytotoxic agent.

Hamann et al., Bioconjugate Chem., 2002, 13, at 45.

The review article by Nagahiro Saijo in Cancer Science, 2004, 95(10), 772-776, that was cited by the Examiner in the prior Office Action dated August 17, 2006, further undermines the Examiner's assertion that one of ordinary skill in the art at the time the invention was made

would have had a reasonable expectation of success that a subject with a B-cell malignancy could be effectively treated with a composition comprising a calicheamicin-anti-CD22-antibody conjugate alone or in combination with one or more cytotoxic or bioactive agents. Saijo's review highlights the high failure rate of molecular-target-based cancer drugs in phase III human clinical trials, even though preclinical results for these potential cancer drugs were positive.

Neither Goldenberg nor Trail et al. teach or describe a method of treating a subject with a B-cell malignancy by administering a composition comprising a calicheamicin-anti-CD22-antibody conjugate alone or in combination with one or more cytotoxic or bioactive agents. Applicants respectfully submit that Goldenberg in view of Trail et al. provide at best a motivation to try to develop a method to treat subjects with a B-cell malignancy by administering a composition comprising a calicheamicin-anti-CD22-antibody conjugate alone or in combination with one or more cytotoxic or bioactive agents, but Goldenberg in view of Trail et al. does not provide a reasonable expectation of success. Applicants respectfully submit that a prima facie case of obviousness has not been made by the Examiner.

With respect to the rejection of claims 134 to 135 under 35 U.S.C. § 103(a) as being unpatentable over Goldenberg in view of Trail et al. and in further view of Maloney et al., the Examiner states that Goldenberg in view of Trail et al. teach a method of treating a B cell malignancy in a patient comprising administering a therapeutically effective amount of an anti-CD22 antibody immunoconjugate, wherein the immunoconjugate is a conjugate of an antibody component with a calicheamicin derivative, but does not explicitly teach that the immunoconjugate is administered in combination with Rituximab, an anti-CD20 antibody. The Examiner states that Maloney et al. teach a method of treating low-grade Non-Hodgkin's lymphoma by administering to a patient a therapeutically effective amount of rituximab, an anti-CD20 antibody, citing the abstract. The Examiner states it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the method of treating Non-Hodgkin's lymphoma comprising administering an immunoconjugate comprising an anti-CD22 antibody as taught by Goldenberg in view of Trail et al. with Rituximab in view of Maloney et al.'s teachings that Rituximab is effective at treating Non-Hodgkin's lymphoma because each of the agents have been individually taught in the prior art for the treatment of lymphoma.

As discussed earlier in this Amendment and Response, neither Goldenberg nor Trail et al. teach or describe a method of treating a subject with a B-cell malignancy by administering a composition comprising a calicheamicin-anti-CD22-antibody conjugate alone or in combination with one or more cytotoxic or bioactive agents, and there is no reasonable expectation of success in treating such subjects based on the teachings of Goldenberg in view of Trail et al. and the state of the art at the time the invention was made. Maloney et al. does not supply the necessary teachings, alone or when combined with Goldenberg in view of Trail et al. One skilled in the art at the time the invention was made would not have a reasonable expectation of success that a subject with a B-cell malignancy could be effectively treated by administering a composition comprising a calicheamicin-anti-CD22-antibody conjugate with an anti-CD19, anti-CD20 or anti-CD33 antibody based on the teachings of Goldenberg in view of Trail et al. in further view of Maloney et al. for the reasons discussed above. Applicants submit that a prima facie case of obviousness has not been established by the Examiner.

By reason of the foregoing, applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 124 to 127, 129 to 133 and 142 to 143 and the rejection of claims 134 to 135 as obvious under 35 U.S.C. §103(a).

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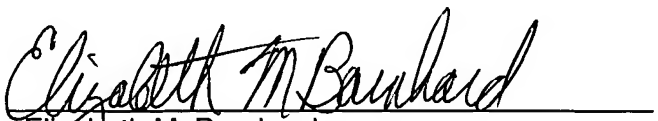
In view of the foregoing discussion, applicants submit that the present application is in condition for allowance. Reconsideration and allowance are respectfully requested.

If a telephone conference would advance prosecution of this application, the Examiner is invited to telephone the undersigned at (845) 602-1842.



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